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TITLE: VAGUS NERVE STIMULATION: A NON-INVASIVE TREATMENT TO IMPROVE THE HEALTH OF GULF VETERANS WITH GULF WAR ILLNESS

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Gulf War Illness (GWI) is a condition occurring in some veterans who served in the 1990-91 Gulf War. To date there is no specific treatment for it. A major complaint of veteran subjects with GWI is widespread pain and achiness. Currently, some drugs are available to treat these symptoms, but these treatments have three major drawbacks – they do not work on all patients; their effect often does not last more than a few months; and the side effects they produce are often so bad that patients stop taking them. The purpose of this study is to test a new method of treating the widespread pain complaint of Gulf Veterans with GWI using a hand-held neuro-stimulator device that activates a nerve in the neck called the vagus. This study will determine if the active device (which does stimulate the vagus nerve) reduces widespread pain in Veterans with GWI in comparison to using an inactive device (which does not stimulate the vagus nerve). We will also test to see if the active device improves migraine which commonly occurs with widespread pain in GWI.

15. SUBJECT TERMS
Gulf War Illness, Vagus Nerve, Neuro-stimulator, Widespread Pain, Migraine

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1. **Introduction:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

   Gulf War Illness (GWI) is a condition occurring in some veterans who served in the 1990-91 Gulf War. To date there is no specific treatment for it. A major complaint of veteran subjects with GWI is widespread pain and achiness. Currently, some drugs are available to treat these symptoms, but these treatments have three major drawbacks – they do not work on all patients; their effect often does not last more than a few months; and the side effects they produce are often so bad that patients stop taking them. The purpose of this study is to test a new method of treating the widespread pain complaint of Gulf Veterans with GWI using a hand-held neuro-stimulator device that activates a nerve in the neck called the vagus. The goal of this study is to determine whether the active device (which does stimulate the vagus nerve) reduces widespread pain in Veterans with GWI in comparison to using an inactive device (which does not stimulate the vagus nerve). We will also test to see if the active device improves migraine which commonly occurs with widespread pain in GWI.

2. **Keywords:** *Provide a brief list of keywords (limit to 20 words)*

Gulf War Illness			
Vagus Nerve			
Neuro-stimulator			
Widespread Pain			
Migraine			

3. **Accomplishments:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction*

   - **What were the major goals of the project?** *List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

     The major research question of this study is to determine if vagus nerve stimulation (VNS) reduces widespread pain of GWI while sham VNS does not. Also, for those veterans with comorbid migraine, the findings of the study will determine if number and severity of migraine headaches are lessened by VNS in contrast to sham VNS.

     The study consists of three Phases:
     Phase 1: Recruitment/Identification at EO VAMC – 7 out of 40 Veterans have been identified and recruited.
     Phase 2: Randomization at MSBI – 3 out of 7 recruited Veterans have been randomized into the study. Of those, 1 participant withdrew.
     Phase 3: Open label – no Veterans have entered this phase of the study yet; the first participant will enter this phase around May 30th provided he is eligible.

   - **What are accomplished under these goals?** *For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the*

methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

❖

Major Activities: We continue to recruit Gulf War veterans with GWI from the War Related Illness and Injury Study Center (WRIISC). At this point we screened 18 possible participants, only 7 were eligible to participate. Of those seven, two were excluded due to not meeting the pain severity requirement. One subject's participation in the study had to be postponed due to surgery. Another subject was contacted to come to Mount Sinai Beth Israel (MSBI) multiple times but he could not be reached.

Eligible veterans are then asked to visit Mount Sinai Beth Israel (MSBI) for the randomization phase and open label phase. So far 3 Veterans have been randomized, 2 are in Phase 2 of the study, of those 1 will enter Phase 3 of the study about May 30, 2017.

Continuation Reviews, amendments, and reports are prepared and submitted to the FDA, DoD, and respective local IRB's (VANJHCS and MSSM).

Specific Objectives: Specific aims: (1) To conduct a small randomized clinical trial (n<44) to evaluate the efficacy of self-administered, non-invasive, active nVNS in veteran with GWI as compared to sham treatment. (2) To provide clinical proof-of-principle data and support future development of broader efficacy studies for GWI. (3) To study a novel therapeutic approach to innovative treatment that has been utilized in multiple forms of headache and fibromyalgia but not been studied in veterans with GWI.

Significant Results or Key Outcomes: No significant results or key outcomes to report at this time.

Other Achievements: No other achievements to report at this time.

❖ **What opportunities for training and professional development has the project provided?**

- *If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state, "Nothing to Report".*
- *Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

Nothing to report.

❖ **How were the results disseminated to communities of interest?**

- *If there is nothing significant to report during this reporting period, state "Nothing to Report".*
- *Describe how the results were disseminated to communities of interest. Include outreach activities that were undertaken to reach members of communities who are not usually*

aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and humanities.

Nothing to report.

❖ **What do you plan to do during the next reporting period to accomplish the goals?**

- *If this is the final report, state "Nothing to Report".*
- *Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

We plan to continue to recruit more subjects into the study. This will be accomplished by introducing the study to Gulf War Veteran support groups at local VA hospitals, calling veterans who have consented in being contacted for future research opportunities, using existing databases that were designed to match the study to eligible and interested veterans.

We also plan to remove the suicidality measure that is currently in the study and that was taken over from a previous study protocol used by the device manufacturer in a civilian population. However, the Columbia Suicide Severity Rating Scale (CSSRS) was validated on an inpatient psychiatric population and its structure has proven to be inappropriate for the population of Gulf War Veterans we are recruiting into the study. The CSSRS does rely on clinician judgment, but for this study's purposes, only yes/no answers were allowed to determine study eligibility. Due to this procedural strategy, we feel that we are excluding veterans who could potentially benefit from this study and would have been eligible for the study otherwise.

4. **Impact:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

❖ **What was the impact on the development of the principal discipline(s) of the project?**

- *If there is nothing significant to report during this reporting period, state "Nothing to Report".*
- *Describe how findings, results, techniques that were developed or extended, or other products from the project made an impactor are likely to make an impact on base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American Style).*

Nothing to report.

❖ **What was the impact on other disciplines?**

- *If there is nothing significant to report during this reporting period, state "Nothing to Report".*
- *Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

Nothing to report.

❖ **What was the impact on technology transfer?**

- *If there is nothing significant to report during this reporting period, state "Nothing to Report".*
- *Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*
  - *Transfer of results to entities in government or industry;*
  - *Instances where the research has led to the initiation of a start-up company; or*
  - *Adoption of new practices.*

Nothing to report.

❖ **What was the impact in society beyond science and technology?**

- *If there is nothing significant to report during this reporting period, state "Nothing to Report".*
- *Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world in areas such as:*
  - *Improving public knowledge, attitudes, skills, and abilities;*
  - *Changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
  - *Improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **Changes/Problems:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

❖ **Changes in approach and reasons for change:** *Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

Nothing to report.

❖ **Actual or anticipated problems or delays and actions or plans to resolve them**: *Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

As described above, we are planning to remove the CSSRS from the study protocol.

❖ **Changes that had a significant impact on expenditures:** *Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

No significant impact on expenditures to report.

❖ **Significant changes in use or care of human rights**

No significant changes to report.

❖ **Significant changes in use or care of vertebrate animals.**

N/A

- **Significant changes in use of biohazards and/or select agents.**

  N/A

6. **Products:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

   - **Publications, conference papers, and presentations**. *Report only the major publication(s) resulting from the work under this award.*

     No publications, conference papers, and presentations to report

   - **Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

     No journal publications to report.

   - **Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

     No books or other non-periodical, one-time publications to report.

   - **Other publications, conference papers, and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

     No other publications, conference papers, or presentations to report.

   - **Website(s) or other Internet site(s).** *List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

     ClinicalTrials.gov- is a registry of clinical trials. It is run by the United States National Library of Medicine (NLM) at the National Institutes of Health, and is the largest clinical trials database, currently holding registrations from over 230,000 trials from 195 countries in the world.
     The study (NCT02791893) has not disseminated any results at this time.

- **Technologies or techniques.** *Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.*

  No technologies or techniques to report.

- **Inventions, patent applications, and/or licenses.** *Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

  No inventions, patent applications, and/or licenses to report.

- **Other Products.** *Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *Other.*

  No other products to report.

7. **Participants and Other Collaborating Organizations:**

- **What individuals have worked on the project?** *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-*

	control and constrained coding.
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name:	Benjamin Natelson, MD
Project Role:	Primary Investigator
Researcher Identifier:	N/A
Nearest person month worked:	12
Contribution to Project:	Dr. Benjamin Natelson is the Primary Investigator for this study. He is responsible for the conduct of the study.
Funding Support:	N/A

Name:	Michelle Blate, APN
Project Role:	Nurse Practitioner
Researcher Identifier:	N/A
Nearest person month worked:	12
Contribution to Project:	Ms. Blate is the nurse practitioner for the study. She conducts the brief medical evaluation at MSBI.
Funding Support:	N/A

Name:	Gudrun Lange, Ph.D.
Project Role:	Consultant
Researcher Identifier:	N/A
Nearest person month worked:	12
Contribution to Project:	Dr. Lange consults on regulatory matters.
Funding Support:	N/A

Name:	Diana Vu
Project Role:	Blinded Trainer
Researcher Identifier:	N/A
Nearest person month worked:	12
Contribution to Project:	Ms. Vu trains every randomized veteran on the use of the device and diary.
Funding Support:	N/A

Name:	Sara Tom, MA
Project Role:	Study Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	9
Contribution to Project:	Ms. Tom oversees all aspects of the study administration and implementation.
Funding Support:	N/A

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - *If there is nothing significant to report during this reporting period, state "Nothing to Report."*
  - *If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

Nothing to report.

- **What other organizations were involved as partners?**
  - *If there is nothing significant to report during this reporting period, state "Nothing to Report."*
  - *Describe partner organizations - academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) - that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed. Provide the following information for each partnership:*
    - **Organization Name:**
      - War Related Illness and Injury Study Center (WRIISC)
      - ElectroCore LLC
    - **Location of Organization:** *(if foreign location list country)*
      - VA New Jersey Health Care System, 385 Tremont Ave, 11th Floor, East Orange, NJ 07018
      - 150 Allen Road, Suite 201, Basking Ridge, NJ 07920
    - **Partner's contribution to the project** *(identify one or more)*
      - **Financial support;**
        - N/A
      - **In-kind support** *(e.g., partner makes software, computers, equipment, etc., available to project staff)*;
        - ElectroCore LLC is providing the nVNS devices and related accessories. They also provided use of the secure MERGE database in order to input study data.
      - **Facilities** *(e.g., project staff use the partner's facilities for project activities)*;
        - The WRIISC is providing their facility for recruitment and screening.

- **Collaboration** *(e.g., partner's staff work with project staff on the project)*;
  - N/A
- **Personnel exchanges** *(e.g., project staff and/or partner's staff use each other's facilities, work at each other's site)*;
  - The study coordinator assigned to this study has been working at Mount Sinai Beth Israel and the WRIISC in VANJHCS. This person is responsible for recruitment, screening, data entry, and IRB submissions at both locations. This person is also the point of contact (POC) for veterans enrolled in the study.
- **Other.**
  - N/A

8. **Special Reporting Requirements:**
   - **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ers.amedd.army.mil for each unique award.*

     No collaborative awards to report.

   - **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

     N/A

9. **Appendices:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.***